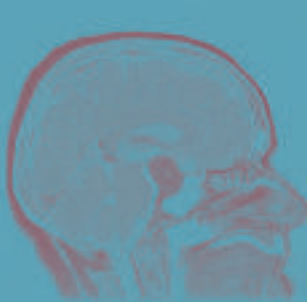




Inside This Issue

Amiodarone and
the Thyroid 2

Inpatient Glycemic
Management:
Safety and Quality
Initiatives at
Mayo Clinic in
Rochester 4

Revised National
Osteoporosis
Foundation
Clinician's Guide
to Prevention
and Treatment of
Osteoporosis 6

Papillary Thyroid Cancer: Keys to a Successful Operation

For over 5 decades, differentiated thyroid carcinoma—of which papillary thyroid carcinoma (PTC) represents more than 90%—has been recognized as one of the least life-threatening malignancies. Although this is usually great news, it has led most investigators to abandon any hopes of developing prospective studies for this disease using disease-related death as an end point. However, interest and investigation of PTC and the proliferation of management guidelines have never been more intense than right now. How can these seemingly conflicting statements be reconciled?

Clive S. Grant, MD, of the Department of Surgery at Mayo Clinic in Rochester, says: “From a surgical perspective, between the 1980s and the turn of the century, the focus of treatment centered on the extent of thyroidectomy. Except for very small PTCs, which could be treated with unilateral lobectomy, total and near-total thyroidectomies were demonstrated to be equivalent and the preferred options. Emerging as the hot new debate was the appropriate extent of associated lymph node

dissection. Previously, lymph node metastases (LNMs) attracted only modest attention for several reasons. Large retrospective studies have consistently failed to identify LNMs as an important prognostic factor; the nodes seem rarely to either progress to or even indicate an increased risk of disease-related death. Former guidelines suggested excision of preoperatively or intraoperatively discovered palpable LNMs.”

Since the turn of the millennium, however, 3 technological advances have driven profound changes in the overall management of PTC:

- Introduction and refinement of high-resolution cervical ultrasonography.
 - Use of recombinant human thyrotropin (TSH).
 - Value and interpretation of serum thyroglobulin.
- The increasing use of these 3 “tools” by endocrinologists across the country has uncovered the frequent reality that LNMs may persist or recur postoperatively, and attempts to ablate them with radioactive iodine treatment are often an unreliable solution. Dr Grant adds: “The whole mindset of treatment has shifted from death (a true rarity) to recurrence (an all-too-frequent event). The changes can be categorized into preoperative, intraoperative, and postoperative phases.”

Preoperative Phase

Dr Grant explains: “To discover LNMs that are macroscopic but not palpable either preoperatively or intraoperatively, we adopted the routine use of preoperative ultrasound when the result of the fine-needle aspiration of a thyroid nodule was either positive or suspicious for PTC. The locations of abnormal-appearing lymph nodes are recorded on



Clive S. Grant, MD

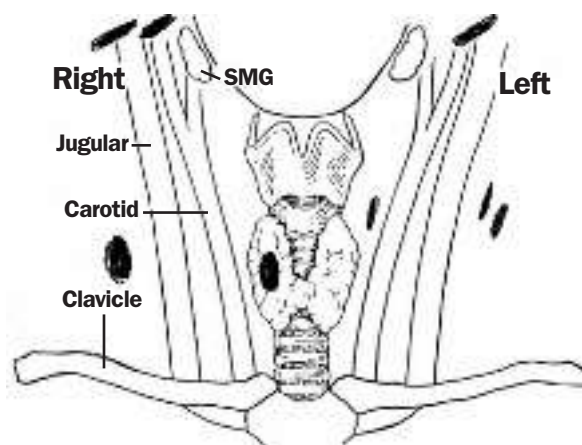


Figure 1. Ultrasound lymph node map. The image depicts not only the known, biopsy-proven papillary thyroid carcinoma in the right thyroid lobe but also a nonpalpable lymph node metastasis (proven by ultrasound-directed fine-needle aspiration biopsy) in the mid right internal jugular chain. The other slender lymph nodes are benign. SMG indicates submandibular gland.

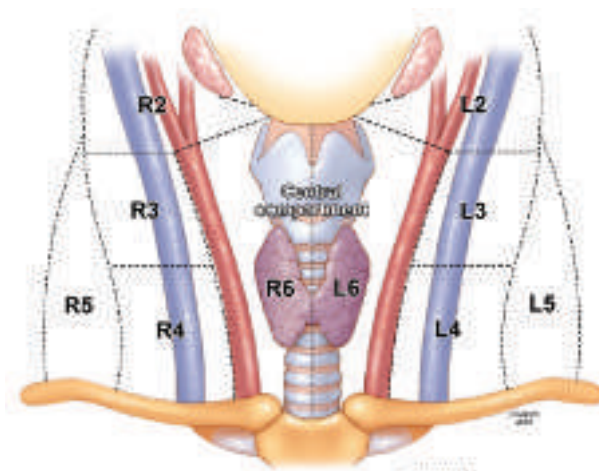


Figure 2. Lymph node compartments of the neck.

a map [Figure 1], which is extremely helpful to the surgeon in planning the extent of lymphadenectomy necessary in conjunction with the thyroidectomy. Of 551 patients undergoing initial operation from 1999 to 2004 at Mayo Clinic, 70 (12.7%) had nonpalpable nodes detected in the lateral compartment, whereas only 10 (1.8%) had similar nodes identified in the central compartment. Even 40% of those patients with palpable abnormal lymph nodes preoperatively benefitted from preoperative ultrasound that altered the operation."

Intraoperative Phase

Dr Grant adds: "Nearly 50% of our patients undergoing initial thyroidectomy for PTC have associated LNMs in the central compartment (compartment 6) [Figure 2], yet preoperative ultrasound is unreliable in identifying these nodes (obscured by the presence of the thyroid gland). Therefore, we have added central compartment lymphadenectomy to the thyroidectomy as the standard operation for PTC. Many of these nodes have proved to be small and would have been potentially overlooked as normal intraoperatively but contain disease histologically. Many times, they may be located adjacent to the recurrent laryngeal nerves,

which require full exposure and careful dissection in all PTC patients.

"Because the high internal jugular lymph nodes (level II) are infrequently involved with PTC and to dissect them requires significant extension of the neck dissection incision, we adopted levels III, IV, and the anterior portion of level V as our standard lateral compartment dissection (so-called modified radical neck dissection). Level II nodes are included in the dissection if palpable or indicated by preoperative ultrasound. Clearly, to rely on the results of ultrasound not only for the presence but also the extent of abnormal lymph nodes requires highly skilled, dedicated, and intellectually committed ultrasonographers. Fortunately, even with the extent of lymph node dissection in the central neck, complications of hypoparathyroidism and recurrent laryngeal nerve damage remain rare."

Postoperative Phase

Across the country, surveillance for disease recurrence has become increasingly intense, incorporating scheduled, routine testing for TSH-stimulated thyroglobulin levels and cervical ultrasonography. With a thyroglobulin level of 2 mcg/L considered the threshold for further imaging investigations for PTC, endocrinologists are discovering recurrent PTC LNMs even smaller than 1 cm. This small size mandates careful preoperative imaging and thorough intraoperative surgical excision of all PTC.

Dr Grant concludes: "Using this surgical approach in 421 patients who received operations at Mayo Clinic from 1999 to 2006, with a median follow-up of 3.3 years, recurrence has been prevented in 96% of patients, where the extent of disease was accurately defined and potentially curable by neck surgery. Ultrasound had a false-negative rate of only 4%, and both permanent hypoparathyroidism and recurrent laryngeal damage occurred in less than 1%."

Amiodarone and the Thyroid

Amiodarone was introduced in Europe in the late 1960s and in the United States more than a decade later for the management of refractory atrial and ventricular arrhythmias. Michael D. Brennan, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester,

explains: "It is a heavily iodinated compound (37% of molecular weight). A 200-mg tablet contains 75 mg of iodine—10% of which is liberated as free iodide daily, resulting in tremendous expansion of the iodine pool. Amiodarone is very lipophilic, which accounts for its extremely long biologic half-



Michael D. Brennan, MD

life—measured in months. Although it is an effective antiarrhythmic agent, its use carries serious potential side effects, including pulmonary toxicity, liver dysfunction, and neuropathy. Amiodarone also has a number of effects on thyroid hormone economy and metabolism, as well as direct effects on the thyroid gland.”

Some predictable effects of amiodarone treatment include the following:

- Increased thyroid gland iodine content and a histologic appearance of abundant colloid and flattened follicular epithelium.
- Inhibition of type 1 deiodinase in the liver, muscle, and other tissues, resulting in a 10% increase in serum free thyroxine (T_4), a 60% decrease in serum triiodothyronine (T_3), and a 150% increase in serum reverse T_3 .
- Inhibition of type 2 deiodinase in the pituitary gland, resulting in a modest increase in serum thyrotropin (TSH). However, in the absence of underlying autoimmune thyroid disease, TSH concentration usually remains within the normal range.
- A 30-fold increase in urinary iodine excretion, a 50-fold increase in plasma inorganic iodide concentration, and a decreased thyroid uptake of administered radioactive iodine (^{131}I).

Patients treated with amiodarone are at risk for development of either hypothyroidism or hyperthyroidism—both of which have serious implications among patients with underlying cardiac disease. The onset of either condition may be considered unpredictable, although screening for certain identified predisposing risk factors should be done before initiation of therapy with amiodarone (Table).

Amiodarone-Induced Hyperthyroidism

Two varieties of amiodarone-induced hyperthyroidism (AIT)—referred to as type I and type II—have been identified. The incidence of AIT is greater in Europe (15%) than in more iodine-replete regions of the world, such as North America (3%). Dr Brennan explains: “It is important to distinguish between AIT type I and type II, because management options may differ. AIT type I has many of the features of so-called Jod-Basedow, or iodine-induced, hyperthyroidism because it occurs among patients with preexisting nodular goiter and frequently in areas of relative or absolute iodine deficiency. The nodules of such thyroid glands lose the ability to autoregulate the amount of iodine that is trapped, organified, and incorporated into thyroid hormone. Thus, patients should be assessed for the presence of nodular goiter before amiodarone

administration [Table]. The presence of a goiter is not of itself a contraindication to the administration of iodine-rich amiodarone, but careful monitoring of thyroid function is essential—particularly during the early weeks and months of therapy.”

AIT type II occurs abruptly and without warning in patients who do not have recognizable preexisting thyroid disease. The onset may occur months or even years after initiation of amiodarone therapy; the average interval is 12 months. Weight loss, muscle weakness, and the reemergence of cardiac arrhythmias are the most frequent symptoms. In these cases, the thyroid gland is nontender and may be mildly enlarged. Laboratory testing shows decreased serum TSH concentration and increased concentrations of total T_4 and free T_4 . The histologic findings are those of widespread follicular distortion and disruption and fibrotic scarring. Dr Brennan adds: “This histologic picture is unique to AIT type II and led us to consider the possibility of a direct toxic effect on the thyroid. We completed *in vitro* studies that confirmed that amiodarone had a direct toxic effect on thyroid cells grown in culture—effects that could be prevented by the prior incubation of the cells with dexamethasone. Thyroid ultrasound in patients with AIT type II shows decreased or absent vascularity; in patients with AIT type I, thyroid nodules and increased vascularity are typically seen.”

The management of AIT is challenging because treatment options are limited by the marked drug-induced expansion of the iodine pool, resulting in ^{131}I uptake of 1% to 2%—levels that preclude its use in therapy. However, some patients with AIT type I may have ^{131}I uptake into the nodules that makes such treatment possible. In addition, antithyroid drugs (eg, thioamides) are less effective in states of high thyroid iodine content. Carole A. Warnes, MD, of the Division of Cardiovascular Diseases at Mayo Clinic in Rochester, comanages many of these cases with Dr Brennan and explains: “Treatment decisions need to take into account the general clinical status of the patient, the presence and degree of cardiac decompensation, and the need for rapid reversal of the hyperthyroid state. If the hyperthyroidism is mild and the cardiac status is stable, drug discontin-



Carole A. Warnes, MD

Table. Checklist for the Clinician Before Starting Amiodarone Therapy

- **Medical history:** discuss any prior history of thyroid disease
- **Physical examination:** thyroid palpation (eg, size, consistency, nodules)
- **Blood tests:** thyrotropin, thyroperoxidase antibodies, free thyroxine

uation may be considered while recognizing that weeks or even months may pass before a euthyroid state is achieved.”

They point to other treatment options for patients with more severe hyperthyroidism or cardiac decompensation, or both. Some patients have such a tenuous cardiac state that amiodarone is the only drug which maintains sinus rhythm and keeps them from heart failure, and in these circumstances amiodarone may need to be continued. Drs Brennan and Warnes emphasize: “Treatment decisions should be customized and made in collaboration between cardiology and endocrinology, and those options include thioamides, glucocorticoids, and thyroidectomy. Potassium perchlorate may hasten recovery in some patients, but it is now difficult to obtain. Antithyroid drugs are more effective in AIT type I than in AIT type II and, if used, require relatively high doses. Glucocorticoids are usually rapidly effective but must be used with caution in patients with cardiac decompensation. Thyroidectomy rapidly reverses hyperthyroidism and has been adopted

successfully in selected cases.”

Amiodarone-Induced Hypothyroidism

In contrast to AIT, the prevalence of hypothyroidism among amiodarone-treated patients is higher in iodine-replete regions, such as North America. Pre-existing autoimmune thyroid disease—such as Hashimoto’s thyroiditis—is a recognized risk factor because the thyroid glands of such patients have an impaired autoregulatory capability. It is prudent, therefore, to screen for the presence of thyroperoxidase antibodies, in addition to serum TSH, before starting amiodarone treatment (Table). If thyroperoxidase antibodies are present, close monitoring for evidence of hypothyroidism is recommended. Amiodarone-associated thyroid failure is treated in a manner similar to treatment of other forms of hypothyroidism, although slightly greater serum TSH values may be expected and tolerated when hypothyroidism is treated with levothyroxine replacement therapy.

Inpatient Glycemic Management: Safety and Quality Initiatives at Mayo Clinic in Rochester



Ananda Basu, MBBS

Optimum management of glycemia in the adult hospitalized patient (Table) is increasingly recognized as an important therapeutic goal. Inpatient hyperglycemia has been linked to unfavorable clinical outcomes related to various patient-important end points, including death, infection, postoperative complications, length of hospital stay, and continued morbidity after dismissal from the hospital. Ananda Basu, MBBS, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: “Effective management of hyperglycemia in critically ill patients with intra-

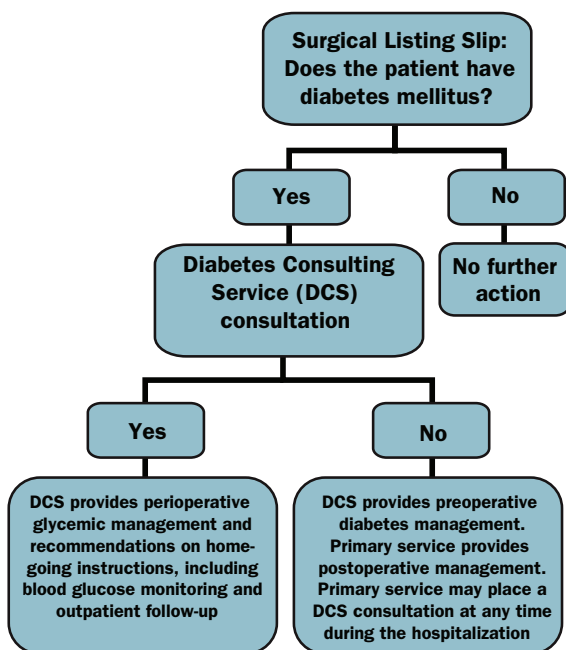
venous insulin infusion in medical and surgical intensive care units has been suggested to improve mortality and morbidity rates. However, similar studies targeting glycemic control with subcutaneous insulin therapy are lacking for hospitalized patients receiving general care. Guided by recommendations from specialty organizations and a strong desire to provide excellent and comprehensive care to hospitalized patients with diabetes mellitus, we have implemented a number of safety and quality initiatives.

“A multidisciplinary Hospital Diabetes Oversight Group was formed and charged with improving the care of the hospitalized patients with diabetes mellitus or hyperglycemia at Mayo Clinic in Rochester. The group includes representatives from endocrinology, hospital internal medicine, critical care medicine, nursing, pharmacy, laboratory medicine, and dietetics departments. Its overall goals are to improve systems of care for patients with diabetes, reduce the risk for errors, minimize the rates of hypoglycemia and hyperglycemia, and coordi-

Table. Premeal Glycemic Targets for the Adult Hospitalized Patient

Patient Group	Glycemic Target, mg/dL		
	ADA	ACE	Mayo Clinic in Rochester
Critically ill	Approximately 110	<110	80-130
Noncritically ill	90-130	<110	80-150

Abbreviations: ACE, American College of Endocrinology; ADA, American Diabetes Association.

Figure. Optimal Perioperative Process for the Patient With Diabetes Mellitus

nate efforts related to diabetes care across the multi-specialty practice.”

Perioperative Glycemic Management

Dr Basu explains: “After examining the current perioperative processes for managing the care of patients with diabetes mellitus, we identified opportunities for improvement in identification and management of glycemic control. A Perioperative Diabetes Management Work Team was created to develop an efficient system for providing care to the diabetic patient who presents for a surgical procedure. The revised perioperative process for diabetes care was designed to optimize the expertise of the Diabetes Consulting Service (DCS) staff while improving communication between the consulting service, the primary services, and the care providers. It requires the surgeon to identify a patient with diabetes when listing the patient for surgery. The surgeon then has the option to consult DCS for perioperative glycemic management and recommendations on home-going instructions, including blood glucose monitoring and outpatient follow-up [Figure].”

Monica R. Sieg, CNP, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, adds: “Since the implementation of the process in September 2007, communication has improved between surgical areas, primary services, and DCS. Streamlining the perioperative process of the patient with diabetes has

provided practice consistency and clear role delineation. An additional enhancement undertaken in glycemic management is standardized appointment-related instructions for patients with diabetes who must fast for certain tests and procedures.”

Treatment of Hyperglycemic Emergencies

Dr Basu notes: “Hyperglycemic emergencies related to diabetes are fairly unique clinical situations with a constellation of associated metabolic abnormalities. Because hyperglycemic emergencies are infrequent and can occur on any inpatient unit, standardization of care is important in ensuring that interventions are provided in an expedited manner. An order set was developed for treatment of adult patients with diabetic ketoacidosis or hyperglycemic hyperosmolar state and provides guidelines for diagnosis, monitoring, and care of patients with either condition. The order set is designed to be initiated in the emergency department and continued on the inpatient unit.”

Computer-Based Monitoring System

Because of the increasing prevalence of hyperglycemia and diabetes in the inpatient setting and the high-risk nature of medications used to treat these conditions, ensuring safety and quality in diabetes medication ordering is a high priority. According to Dr Basu: “Diabetes in patients receiving diabetes-related medications is managed by various care providers. To offer oversight for safe and effective diabetes management, we implemented a computer-based monitoring system for the hospital setting. A series of simple ‘rules’ related to diabetes medications, glucose monitoring, and blood glucose levels were programmed. These rules are fed into a series of databases. When the conditions of a rule are met, a report is generated for follow-up. The reports are monitored daily and providers are contacted with suggestions to improve patient safety or glycemic control, or both. This system has been very well



Monica R. Sieg, CNP, and Julie Brown, CNS

received by health care providers and should improve glycemic control, promote appropriate and safe insulin use in the hospitals, and improve quality of care.”

Management of Continuous Subcutaneous Insulin Infusion Pumps in the Hospital

Management of care for patients admitted to the hospital with a continuous subcutaneous insulin infusion (CSII) pump is particularly challenging for providers without diabetes expertise. Julie Brown, CNS, of the Department of Nursing at Mayo Clinic in Rochester, explains: “Often, patients wish to continue their treatment with the pump and to self-manage their diabetes care. Some patients are well versed in insulin pump management; others lack knowledge or experience in managing their diabetes by using an insulin pump. In addition, health

care providers may not be familiar with insulin pump concepts or the operation of an insulin pump.

“To address these issues, an institutional policy was developed that describes management of a CSII pump in the hospital. All patients desiring to continue the use of their CSII pump during their hospitalization are seen in consultation by the DCS. The patient’s knowledge about the pump, recent glucose control, and ability to manage the pump are assessed, and a determination about pump use in the hospital is made. For hospitalized patients who continue to use the CSII pump, the policy provides guidance for insulin ordering, glucose testing, pump refills, site changes, and documentation of pump rates. While in the hospital, patients are observed closely by the DCS staff to determine their continued ability to self-manage the pump, as well as whether adjustments to pump rates are required.”

Revised National Osteoporosis Foundation Clinician’s Guide to Prevention and Treatment of Osteoporosis

There is general agreement that pharmacologic therapy should be considered for patients with osteoporosis as defined by the World Health Organization (WHO) criteria: patients with a bone mineral density (BMD) T-score of -2.5 or less at the femoral neck, total hip, or spine and patients who present with low-trauma fractures of the spine or hip (so-called established osteoporosis). More controversial is the optimal management of approximately 34 million people in the United States who have a proximal femur T-score between -1.0 and -2.5 and are classified as having low bone mass, or *osteopenia*. Analogous to prehypertension and impaired fasting glucose, osteopenia is an intermediate-risk condition that, because of its high prevalence relative to persons with osteoporosis, actually accounts for most fractures in the community.

Sundeep Khosla, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “The fundamental problem is that BMD is only 1 risk factor for fracture, and there is a wide spectrum of fracture risk within the large pool of individuals with osteopenia. Basing therapeutic decisions principally on risk stratification with BMD T-scores—as has been the practice until recently—fails to optimally target drug therapy to those individuals most likely to have a fracture, since BMD T-scores convey no direct information regarding the absolute likelihood of fracture.”



Sundeep Khosla, MD, and L. Joseph Melton, III, MD

To address this issue, the WHO commissioned the development of a fracture prediction algorithm, FRAX, which calculates the 10-year probability of a hip fracture or any major osteoporotic fracture (defined as clinical vertebral, hip, forearm, or humerus fracture) taking into account the patient’s femoral neck BMD and risk factors. L. Joseph Melton, III, MD, of the Division of Epidemiology at Mayo Clinic in Rochester, says: “Similar to risk stratification models for heart disease and breast cancer, the FRAX algorithm incorporates clinical risk factors that are relatively easy to measure in practice and impact fracture risk independently of BMD.” The risk factors selected for use in the FRAX algorithm are age, sex, personal history of a prior osteoporotic fracture (including an incidentally noted vertebral

deformity on spine radiographs), long-term use of oral glucocorticoids, rheumatoid arthritis, other secondary osteoporosis, and a parental history of hip fracture, as well as low body mass index, current cigarette smoking, and excessive alcohol intake (3 or more drinks per day).

The National Osteoporosis Foundation (NOF) subsequently appointed a Guide Committee to revise the Clinician's Guide to Prevention and Treatment of Osteoporosis (www.nof.org). The committee is also to collaborate with the WHO to calibrate the FRAX algorithm for use in the United States by incorporating country-specific data on hip fracture incidence and mortality rates. The overall approach outlined in the new NOF Guide involves a detailed history and physical examination, together with BMD assessment and, where appropriate, use of the FRAX 10-year estimated fracture probabilities, to establish a patient's fracture risk. The NOF recommends that all postmenopausal women and older men be evaluated clinically for osteoporosis risk to determine the need for BMD testing. The femoral neck BMD T-score is then entered into the FRAX calculator, along with the pertinent clinical risk factors, to arrive at the 10-year probability of a hip fracture, as well as the probability of any major osteoporotic fracture. The US-adapted FRAX algorithm is available on the NOF Web site and at www.shef.ac.uk/FRAX.

Dr Melton notes: "The NOF Guide Committee also performed an economic analysis to identify levels of fracture risk above which it is cost-effective to consider pharmacotherapy in this country." Based on certain assumptions (ie, drug costs of \$600 per year, treatment for 5 years followed by no drug therapy for the next 5 years, overall fracture risk reduced 35% by treatment, and cost-effectiveness at \$60,000 per quality-adjusted life-year gained), the economic model led to recommendations that postmenopausal women and men age 50 years and older should be considered for drug treatment if they already have a hip or vertebral fracture; if their BMD T-score at the femoral neck, total hip, or spine is -2.5 or less; or if they have a T-score between -1.0 and -2.5 combined with a 10-year probability of hip fracture of 3% or greater or a 10-year probability of a major osteoporotic fracture of 20% or greater based on the US-adapted FRAX algorithm. Although these thresholds take treatment cost-effectiveness into account, Dr Melton stresses that "recommendations in the NOF Guide are intended to serve as a reference point for clinical decision making with individual patients. They are not intended to be rigid standards or rules, and they should not be

interpreted as quality standards or used to limit coverage for treatments."

Dr Khosla highlights: "It is important for the physician to be aware of certain caveats in using the FRAX algorithm. The algorithm is intended only for postmenopausal women and for men age 50 years and older, it applies only to previously untreated patients, and it uses femoral neck BMD. Although total-hip BMD may be substituted, the algorithm has not been validated for the use of spine BMD. Finally, it uses a single reference standard (the reference values of the Third National Health and Nutrition Examination Survey [NHANES III] for a young white woman, which are derived from a Hologic instrument [Hologic Inc. of Bedford, Massachusetts]) to calculate T-scores.

"The use of this reference standard is somewhat problematic because the database used in the FRAX calculation is slightly different from that used in current Hologic densitometers, and T-scores from other densitometers may differ from the Hologic T-score. Moreover, many densitometers use a male normative database for men, and some centers use ethnic-specific databases for T-score calculations. However, adjustments for race and sex are built into the FRAX model, so these T-scores are inappropriate. To address these issues, a FRAX Patch tool has been developed (available at www.nof.org/frax_patch.htm). It allows the physician to specify the densitometer used and the actual BMD in g/cm^2 , and the tool then provides a T-score that is appropriate to enter into the FRAX calculator. Efforts are currently underway to have the densitometer manufacturers directly provide FRAX-compatible T-scores."

Dr Khosla concludes: "These caveats notwithstanding, a major advantage of the FRAX algorithm is that it provides both physician and patient with a much better understanding of the patient's likelihood of having a fracture—absolute (%), as opposed to relative, fracture risk—than otherwise possible. Combined with the relative risk reduction achievable with therapy, this risk value reveals the extent to which the patient's 10-year fracture probability could be improved by adhering to long-term treatment. Using this shared decision-making approach, the patient and the physician can weigh the potential fracture risk in the absence of treatment against the benefits of treatment with different drugs and versus possible adverse effects and costs. This comparison should lead to a more educated decision regarding whether to initiate drug treatment and will be especially valuable in cases where fractures have not yet occurred and the patient's BMD is in the osteopenic range."

Upcoming Education Opportunities

Mayo Clinic Nutrition in Health and Disease. September 24-25, 2009, Graves 601 Hotel, Minneapolis, Minnesota. This course, designed for physicians, dietitians, nurses, and pharmacists, will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

12th Mayo Clinic Endocrine Course

March 16-20, 2009, on the Big Island of Hawaii. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The 5-day course (7:30 AM to 12:30 PM daily) will span the full spectrum of endocrinology. The course will be held at the Hapuna Beach Prince Hotel. Located at the Mauna Kea Resort complex on the Kohala Coast of the Big Island of Hawaii, this spectacular resort is a 30-minute drive from the Kona International Airport at Keahole. For more information about this course, please visit <http://endocourse.mayo.edu>.



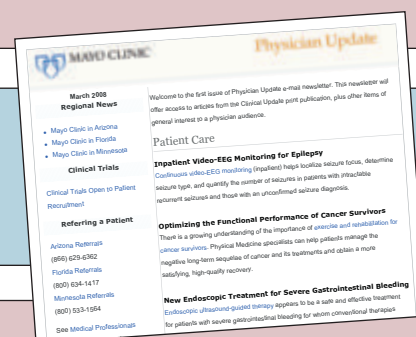
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